REMARKS

Upon entry of this Amendment, claims 40, 41, 45, 47, 54, 56, 57, 59, 62-63, 68, 70, 72, 75, 76, 78, and 80-139 will be pending in the present application. Claims 40, 45, 47, 54, 56, 57, 59, 62, 63, 70, 75, 76, 78, and 80 have been amended. The amendments to the claims are fully supported by the specification as filed. Claims 81-139 have been added herein. The new claims are fully supported by the specification as filed. No new matter has been introduced. Claims 38, 39, 42, 44, 48, 50, 51, 53, 60, 61, 64-66, 71, 73, 74, 77, and 79 are canceled without disclaimer or prejudice to reintroduction at a later time.

The specification has been amended to update the priority information and to insert the ATCC's current contact information. Additionally the specification has been amended to correct an obvious typographical error in which two residues of SEQ ID NO:10 were inadvertently juxtaposed. The correct sequence is supported by Figures 3 and 4 of the application as filed. A Substitute Sequence Listing reflecting the correction to the sequence and a Statement to Support Submission are submitted herewith. SEQ ID NOs: 11-24 also have been added to the sequence listing, as supported by the original sequence listing, specification, and figures of the application as filed. SEQ ID NOs are being assigned to these sequences as a means of simplifying their recitation in the claims.

SEQ ID NO:11 is the polynucleotide sequence of the repeat insert, identified for strain G39, shown in Figure 3. SEQ ID NO:12 is the polypeptide sequence of the repeat insert, identified for strain G39, shown in Figure 3. SEQ ID NO:13 is the polynucleotide sequence encoding the D1 motif shown in Fig. 3. SEQ ID NO:14 is the polypeptide sequence of the D1 motif shown in Figure 3. SEQ ID NO:15 is the polynucleotide sequence encoding the D2 motif shown in Figure 3. SEQ ID NO:16 is the polypeptide sequence of the D2 motif shown in Figure 3. SEQ ID NO:17 is the polypeptide sequence of the D3 motif shown in Figure 3. SEQ ID NO:18 is the polynucleotide sequence encoding the D3 motif identified in the strain G39 repeat shown in Figure 3. SEQ ID NO:19 is the polynucleotide sequence encoding SEQ ID NO:9, shown twice in Figure 4C, spanning nucleotides 2641 – 2676 and nucleotides 2776 – 2811 of SEQ ID NO:4. SEQ ID NO:20 is the polynucleotide sequence encoding SEQ ID NO:10, shown in Figure 4D, spanning nucleotides 3202 - 3216 of SEQ ID NO:4. SEQ ID NO:21 is the polynucleotide sequence encoding SEQ ID NO:10, shown in Figure 4C and spanning nucleotides 3259 – 3273 of SEQ ID NO:4.

SEQ ID NO:22 is the polynucleotide sequence encoding the D3 motif identified in strain CCUG 17874 (see Figure 3), spanning nucleotides 3358 – 4402 of SEQ ID NO:4, as shown in Figures 4D and 4C. SEQ ID NO:23 is the peptide motif of 6 contiguous asparagines shown in Figures 4C and 4D (amino acid residues 880– 885 of SEQ ID NO:5) and described on page 53 of the specification. SEQ ID NO:24 is the polynucleotide sequence encoding the peptide motif of 6 contiguous asparagines (nucleotides 3172 – 3189 of SEQ ID NO:4) shown in Figures 4C and 4D and described on page 53.

A paper copy of the Substitute Sequence Listing is attached hereto. Also provided is a diskette containing a computer readable form of the substitute Sequence Listing. The information recorded in the computer readable form is identical to the paper copy of the Substitute Sequence Listing. Entry of the Substitute Sequence Listing is respectfully requested.

The Specification was further amended to indicate the proprietary nature of several trademarks. Applicants assert that the amendments to the specification are fully supported by the specification as filed and that no new matter has been added to the application.

Applicants note with appreciation the grant of the Request for Continued Examination and entry of the prior Amendment. The acknowledgment of Applicants' submission of the executed Covacci declaration is also noted with appreciation. Applicants further note with appreciation the Examiner's withdrawal of the enablement rejection and of the art-based rejections in view of Cover *et al.* (Office Action at pages 5-6) and consideration of the Supplemental Information Disclosure Statement.

Applicants acknowledge that the objection to the drawings made in the Office Action dated February 14, 2000 has been maintained. Fourteen pages of formal drawings corresponding to Figs. 1-5 have been submitted to the Drawing Review Branch, accompanied by a copy of the Notice of the Draftsperson's Patent Drawing Review dated August 20, 1999, under 37 C.F.R. § 1.84. Applicants request entry of the formal drawings.

Applicants traverse the restriction requirement for the reasons already of record. Nonetheless, to advance the application to issuance, claims 64 and 65 have been canceled without disclaimer or prejudice to reintroduction at a later time.

I. THE CLAIMS SATISFY THE REQUIREMENTS OF 35 U.S.C. § 112, SECOND PARAGRAPH.

Claim 40 has been rejected as allegedly indefinite in the recitation of "antigen comprising SEQ ID NO:5." Although Applicants do not accede to the stated ground of rejection, it is respectfully noted that claim 40 has been amended to recite the "CAI antigen comprising the amino acid sequence of SEQ ID NO:5." Claim 40 also has been amended to omit the term "the."

Claims 60 and 62 have been rejected as allegedly being indefinite in the recitation of the phrase "a purified polypeptide of the *Helicobacter pylori* CAI antigen." The rejection as to claim 60 is not at issue as that claim has been canceled. Applicants traverse the rejection of pending claim 62. The subject terminology is sufficiently clear to convey the metes and bounds of the invention to one of skill in the art. It is clear from the specification that the term "CAI antigen" includes the full length polypeptide and fragments and derivatives thereof. (Specification as filed at page 6, lines 12-15.) Nevertheless, to advance the application to issuance, Applicants have amended claim 62 to clarify that the purified polypeptide has at least ten contiguous amino acids of SEQ ID NO:5, thus including polypeptide fragments and derivatives thereof, for example allelic variants and chemically modified polypeptides.

Claims 42, 45, 48, 51, 54, 61-63, 70, 73, 75, and 77-79 have been rejected as allegedly indefinite in the recitation of the phrase "exhibits no functional contribution to toxicity, or substantially reduced functional contribution to toxicity." In particular, the Examiner asserts that the phrase renders the claims indefinite in that it is allegedly unclear "what function does not contribute, or does show substantially reduced functional contribution to toxicity." The rejection as to claims 42, 48, 51, 61, 73, 77, and 79 is not at issue as those claims have been canceled. With regard to the pending claims, the subject terminology is sufficiently clear to convey the metes and bounds of the invention to one of skill in the art. Nonetheless, to advance the application to issuance, Applicants have amended the claims to clarify that the recited polypeptide is "substantially noncytotoxic." While newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure, there is no *in haec verba* requirement. MPEP § 2163 I.B. Thus, the phrase "substantially noncytotoxic" is supported in the specification by the phrase "exhibits no functional

contribution to toxicity, or substantially reduced functional contribution to toxicity." That the toxicity of the original phrase refers to cytotoxicity is supported in the specification as filed, for example, at page 50, lines 24-37, in which cytotoxicity, as measured by vacuolizing activity on HeLa cells, is shown to be associated with the presence of the CAI antigen.

For the foregoing reasons, Applicants respectfully request that the rejection of claims 40, 45, 54, 62, 63, 70, 75, and 78 under 35 U.S.C. § 112, second paragraph be withdrawn.

II. THE CLAIMS CONTAIN SUBJECT MATTER ADEQUATELY DESCRIBED IN THE SPECIFICATION.

Claims 45, 54, 62, 68, 75, and 78 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written descriptive support. Specifically, the Examiner alleges that "there appears to be no descriptive support in the instant specification for a polypeptide that comprises at least ten 'contiguous' amino acids of SEQ ID NO:5." (Office Action at page 7.) Applicants traverse.

As previously mentioned, while newly added claim limitations must be supported in the specification, that support may be through express, implicit, or inherent disclosure. There is no *in haec verba* requirement. As disclosed in the specification as filed at page 6, lines 12-15, the term "CAI antigen" includes the full length polypeptide and fragments and derivatives thereof. That the recited ten amino acids of the polypeptide of the claims are adjacent or "contiguous" is inherent in the word "fragment." Thus, the term "contiguous" was described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants had possession of the claimed invention at the time the application was filed. Accordingly Applicants request reconsideration and withdrawal of the rejection.

III. THE CLAIMS ARE ENABLED BY THE SPECIFICATION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH.

Claims 45, 47, 48, 50, 51, 53, 54, 56, 57, 59, 61-63, 70, and 73-80 have been rejected under 35 U.S.C. § 112 for alleged lack of enablement. Specifically, the Examiner alleges that "the instant specification does not provide enablement for such polypeptide fragments having 'at least 10' or 'at least 15' contiguous or discontiguous amino acids of CAI antigen, a polypeptide of SEQ ID NO:5, CT or HSP antigens of

H. pylori having the recited characteristics," the recited characteristics being the ability to induce production of specific antibodies and substantial noncytotoxicity. As to claims 48, 50, 51, 53, 61, 73, 74, 77 and 79 the rejection is not at issue as those claims have been canceled. With regard to the pending claims, Applicants respectfully disagree.

The enablement requirement of 35 U.S.C. § 112, first paragraph, mandates that the specification teach those in the art how to make and use the claimed invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). The test of enablement is not whether any experimentation is necessary but, whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Wands*, 8 U.S.P.Q.2d at 1404.

The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of nonenablement ***must*** be based on the evidence as a whole. *Id.* In order to make a rejection, the examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The burden then shifts to the applicant to provide persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973).

The present invention as defined by the claims is directed to a purified polypeptide having the amino acid sequence of SEQ ID NO:5 and fragments thereof, vaccines containing the polypeptide having the amino acid sequence of SEQ ID NO:5 and fragments thereof, and methods of preparing the vaccines. The Examiner has not established a *prima facie* case of nonenablement of the claims. The skilled artisan would be able to make and use the claimed invention using the application as a guide. Therefore, the claims are enabled by the application. Based on the evidence as a whole, the claims are enabled -- one skilled in the art would be able to make and use the claimed invention.

A. The Application Enables Claims Reciting Polypeptide Fragments Having Immunogenicity.

The Examiner has stated that:

> [i]t is uncertain whether retention of any 10 or 15 contiguous or discontiguous amino acid residues from any part of the CAI antigen , the polypeptide of SEQ ID NO:5, CT or HSP (i.e., terminal or central parts) would yield polypeptides that would have the expected immunogenic functions.

(Office Action at page 8.)

Contrary to the Examiner's implicit assertion that the application must teach how to make and use ***every*** embodiment of the invention, the specification need only disclose one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims to satisfy the enablement requirement. *In re Fischer*, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

MPEP § 2164.02.

The fact that some experimentation may be required is not fatal; the question is whether the experimentation is undue. *Wands*, 8 U.S.P.Q.2d at 1404. Moreover,

"an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224 (C.C.P.A. 1977). Even "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, 8 U.S.P.Q.2d at 1404.

The specification discloses a full length CAI antigen protein used to produce a mouse serum having specificity for the protein as a representative example of the claimed genus of CAI antigen polypeptides that can be used in the invention. No more than routine experimentation is required to determine which polypeptide fragments of the CAI antigen work in the invention -- i.e., to generate antibodies having specificity to *Helicobacter pylori* CAI antigen -- in view of the example provided in the application. The methods for using polypeptide fragments are essentially identical to the methods for using the full length polypeptide. Using the application as a guide, nothing beyond routine experimentation would have been required to produce antibodies to fragments of the CAI antigen.

It is the Examiner's contention, however, that the immunogenicity of polypeptide fragments is unpredictable. The Examiner relies on McGuinnes *et al.* (WO 90/06696) as evidence of this alleged unpredictability. Specifically, the Examiner describes McGuinnes as demonstrating

> that portions of an immunodominant bacterial polypeptide comprising ten contiguous amino acid residues from any random parts of the whole polypeptide molecule do not contain the antigenic epitope(s) that are recognized by the bactericidal (protective) antibodies . . . . *Every 10-mer portions* (sic) on this bacterial polypeptide did not contain such epitope(s) indicating that the prophylactic (protective) or therapeutic efficacy of any fragments from any portion of a bacterial polypeptide antigen is not a predictable event.

(Office Action at page 9.)

With all due respect, the Examiner is asserting the incorrect legal standard for enablement. Enablement does not require 100% success. In *Wands*, the claims were found to be enabled on the basis of only 4 successful tests out of 143 experiments. *Wands*, 8 U.S.P.Q.2d at 1406. Accordingly, McGuinnes supports enablement of the present claims. Several decapeptides disclosed therein reacted with the specific monoclonal antibody. (McGuinnes at pages 45-46; Fig. 5.) While some decapeptides

of McGuinnes reacted more strongly with the antibodies than others did, the strength of the reaction is inconsequential. Detection of any level of reaction indicates success.

Moreover, one having ordinary skill in the art at the time of filing of the application would have been able to determine the efficacy of a polypeptide in inducing an immune response. For example, Manetti *et al.* (*Infection and Immunity*, 63(11): 4476-4480 (1995)) report that administration of cytotoxin protein to rabbits effectively induces a neutralizing response therein.

Applicants submit that a *prima facie* case of nonenablement has not been established. One having ordinary skill in the art would have been able to determine which polypeptides of the invention and fragments thereof are able to induce production of antibodies having specificity therefor. Accordingly Applicants request reconsideration and withdrawal of the rejection.

B. The Application Enables Claims Reciting Polypeptide Fragments that are Substantially Noncytotoxic.

The Examiner alleged that the specification does not teach polypeptide fragments comprising ten or fifteen amino acids of the CAI antigen, the polypeptide of SEQ ID NO:5, CT, or HSP which are nontoxic or substantially less toxic. Applicants respectfully disagree.

The specification discloses a representative example in which the cytotoxicity of CAI antigen was determined by measuring the vacuolizing activity of the polypeptide on HeLa cells. (Specification as filed at page 50.) Nothing more than routine experimentation is required to determine which fragments of the CAI antigen work in the invention in view of the example provided in the application. The methods for using fragments of the CAI antigen are essentially identical to the methods for using the full length polypeptide. The fact that some experimentation may be required is not fatal; the question is whether the experimentation is undue. *Wands*, 8 U.S.P.Q.2d at 1404. Even a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance. *Id.* Using the application as a guide, one of ordinary skill in the art would have been able to determine which polypeptide fragments are substantially noncytotoxic.

The Examiner relies on the specification and on Oderda as teaching that the full length CAI antigen is strongly *associated with* cytotoxicity. That is not to say that the CAI antigen *is* cytotoxic, however.

As the Examiner has failed to establish a *prima facie* case of nonenablement, Applicants request reconsideration and withdrawal of the rejection.

C. The Application Enables Claims Reciting Prophylactic or Therapeutic Vaccines

The Examiner has alleged that the prophylactic and therapeutic vaccines of the invention are not enabled by the specification because the specification "lacks any human or animal data or evidence demonstrating the prophylactic or therapeutic efficacy of the claimed vaccine with or without the second polypeptide, or any serological evidence that is predictive of or correlative with prophylactic and therapeutic efficacy of the vaccine." (Office Action at page 10.) Applicants traverse.

Compliance with the enablement requirement does not turn on whether an example is disclosed. An applicant need not actually have reduced the invention to practice prior to filing. "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987) (quoting *In re Chilowsky*, 229 F.2d 457, 461 (C.C.P.A. 1970). Thus, the application need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970).

Moreover, according to MPEP §2107.03,

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials.... [I]t is improper for office personnel to request evidence...regarding the degree of effectiveness [in humans] (underlining in original).

Enablement requires only that the application teach how to make and use the invention without undue experimentation. This requirement has been met: one having ordinary skill in the art would be able to make and use the invention without undue experimentation using only the application as a guide.

The application contains an enabling disclosure of prophylactic and therapeutic vaccines. The specification teaches that each of the *Helicobacter pylori*

proteins disclosed therein may be used as a sole vaccine candidate or in combination with one or more other antigens. (Specification as filed at page 38.) The vaccines of the invention comprise an immunologically effective amount of the CAI antigen polypeptide and a pharmaceutically acceptable carrier. Various modes of administration are disclosed. (Specification as filed at pages 40-41).

Section 112 requires the specification to be enabling only to persons "skilled in the art to which it pertains, or with which it is most nearly connected." *DeGeorge v. Bernier*, 226 U.S.P.Q. 758 (Fed. Cir. 1985). Thus, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, 231 U.S.P.Q. 649 (Fed. Cir. 1986) ("A patent applicant need not include in the specification that which is already known to and available to the public."); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). A person skilled in the art is deemed to possess not only basic knowledge of the particular art, but also "the knowledge of where to search out information" for section 112 purposes. *In re Howarth*, 210 U.S.P.Q. 689 (C.C.P.A. 1981).

Several pre-filing date references, previously submitted by way of declaration, disclose various animal models for studying the effects of candidate vaccines on *Helicobacter pylori* infection in humans. For example, Krakowka *et al.* (*Infection and Immunity*, 55(11):2789-2796 (1987)) report that *Campylobacter pylori* infection of gnotobiotic piglets reproduces many of the features of diseases associated with *C. pylori* infection of humans. Similarly, Radin *et al.* (*Infection and Immunity*, 58(8):2606-2612 (1990)) disclose that gnotobiotic piglets and gnotobiotic dogs are useful animal models for studying the effects of *Helicobacter pylori* infection in humans. Additionally, Telford *et al.* (*J. Exp. Med.*, 179:1653-1658 (1994)) report the development of a mouse model of human gastric disease as a basis for the understanding of *Helicobacter pylori* infection and for the development of therapeutics and vaccines. Accordingly, it would not have required undue experimentation for one of ordinary skill in the art to determine which vaccines of the invention are prophylactic or therapeutic for *Helicobacter pylori* infection.

In view of the foregoing, Applicants submit that the skilled artisan would be able to make and use the claimed invention using the application as a guide. Consideration of the *Wands* factors weighs in favor of a finding of enablement: (1)

the breadth of the solicited claims with respect to CAI antigen polypeptides having the amino acid sequence of SEQ ID NO:5, CT, HSP, and fragments and derivatives thereof reasonably correlates to the enabling disclosure of the application; (2) animal models for studying *H. pylori* infection were well known to one of skill in the art at the time of filing; (3) one of skill in the art of molecular biology in 1995 was highly sophisticated; (4) the specification as filed provided ample guidance, including examples, to one of skill in the art at the time of filing as to how to make and use the invention; and (5) nothing more than routine experimentation was required to determine which polypeptides and vaccines of the invention work therein.

Applicants submit that the evidence, when considered as a whole, establishes enablement of the solicited claims. Accordingly Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112.

IV. THE REJECTIONS OVER THE CITED PRIOR ART ARE MOOT.

Claims 38, 42, and 44 have been rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Hirschl *et al.* ("Hirschl"). The rejection over Hirschl is moot in view of the cancellation of claims 38, 42, and 44 without disclaimer or prejudice to reintroduction at a later time.

Claims 38, 39, 42, 44, 48, 50, 60, 66, 71, 73, 74, 77, and 79 have been rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by Clayton *et al.* ("Clayton"). Claims 60 and 77 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Clayton. The rejection over Clayton is moot in view of the cancellation of claims 38, 39, 42, 44, 48, 50, 60, 66, 71, 73, 74, 77, and 79 without disclaimer or prejudice to reintroduction at a later time.

Claims 38, 39, 42, 44, 71, 73, and 74 have been rejected under 35 U.S.C. § 102(b), or alternatively 35 U.S.C. § 103(a), as being unpatentable over Tummuru *et al.* ("Tummuru"). The rejection over Tummuru is moot in view of the cancellation of claims 38, 39, 42, 44, 71, 73, and 74 without disclaimer or prejudice to reintroduction at a later time.

Applicants accordingly request withdrawal of the rejections over the cited prior art.

CONCLUSION

Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a notice of allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-568-3100.

Attached hereto is a marked-up version showing changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Date: July 22, 2002

Respectfully submitted,

Felicity E. Groth

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Attachments:

Paper Copy of Substitute Sequence Listing (pages 1-20)
Substitute Sequence Listing in Computer Readable Form
Statement in Support of Submission of Substitute Sequence Listing
Manetti *et al.* (*Infection and Immunity*, 63(11): 4476-4480 (1995)
Version with Markings to Show Changes Made
Associate Power of Attorney

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the application as follows:

IN THE SEQUENCE LISTING:

Please insert pages 1-20 of the Sequence Listing.

IN THE SPECIFICATION:

Please replace the paragraph on page 1 that was added by Preliminary Amendment dated July 26,1999 to the specification before the original first line thereof with the following paragraph:

--This application is a divisional of U.S. application Serial No. 08/471,491, filed June 6, 1995, [now allowed] now U.S. Patent No. 6,090,611, which is a divisional of U.S. application Serial No. 08/256,848, filed October 21, 1994, now abandoned, which is a U.S. national phase application of PCT/EP93/00472, filed March 2, 1993 and PCT/EP/00158, filed January 25, 1993, which two PCT applications claimed priority benefit of Italian application Serial No. FI 92 A 000052, filed March 2, 1992, the entire contents of each application is incorporated by reference herein.--

Please replace the paragraph bridging pages 39-40 with the following:

--Preferred adjuvants to enhance effectiveness of the composition include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (PCT Publ. No. WO 90/14837), containing 5% Squalene®, 0.5% Tween 80®, and 0.5% Span 85® (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalane, 0.4% Tween 80®, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi™ adjuvant system (RAS), (Ribi

Immunochem, Hamilton, MT) containing 2% Squalene®, 0.2% Tween 80®, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (3) saponin adjuvants, such as Stimulon™ (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freunds Adjuvant (CFA) and Incomplete Freunds Adjuvant (IFA); (5) cytokines, such as interleukins (IL-1, IL-2, etc.), macrophage colony stimulating factor (M-CFS), tumor necrosis factor (TNF), etc; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition. Alum and MF59 are preferred.--

Please replace the paragraph spanning from page 52, line 15 to page 53, line 9 with the following replacement paragraph:

--The *cai* gene coded for a putative protein of 1147 amino acids, with predicted molecular weight of 128012.73 Daltons and an isoelectric point of 9.72. The basic properties of the purified protein were confirmed by two dimensional gel electrophoresis. The codon usage and the GC content (37%) of the gene were similar to that described for other *H. pylori* genes (13, 26). A putative ribosome binding site: AGGAG, was identified 5 base pairs upstream from the proposed ATG starting codon. Computer search for promoter sequences of the region upstream from the ATG start codon, identified sequences resembling either -10 or -35 regions, however, a region with good consensus to an *E. coli* promoter, or resembling published *H. pylori* promoter sequences was not found. Primer extension analysis of purified *H. pylori* RNA showed that 104 and 214 base pairs upstream from the ATG start codon there are two transcriptional starts sites. Canonical promoters could not be identified upstream from either transcriptional initiation sites. The expression of a portion of the CAI antigen by clone 57/D suggests that *E. coli* is also recognizing a promoter in this region, however, it is not clear whether *E. coli* recognizes the same promoters of *H. pylori* or whether the *H. pylori* DNA that is rich in A-T provides *E. coli* with regions that may act as promoters. A rho independent terminator was identified downstream from the stop codon. In Fig. 4, the AGGAG ribosome binding site and terminator are underlined, and the repeated sequence and motif containing 6 asparagines are boxed. The CAI antigen was very hydrophilic, and did not show obvious leader peptide or

transmembrane sequences. The most hydrophilic region was from amino acids 600 to 900, where also a number of unusual features can be observed: the repetition of the sequences EFKNGKNKDFSK (SEQ ID NO:9) and EPIYA [EPYIA] (SEQ ID NO:10), and the presence of a stretch of six contiguous asparagines (boxed in Fig. 4).--

Please replace the first paragraph on page 61 of the specification with the following paragraph:

--The following materials were deposited on December 15, 1992 and January 22, 1993 by Bioscine Sclavo, S.p.A.[, the assignee of the present invention,] with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, phone (703) 365-2700, [12301 Parklawn Drive, Rockville, MD, phone (301) 231-5519,] under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for Purposes of Patent Procedure. For the cytotoxin protein (CT):

ATCC No.: 69157 *E. coli* TG1 containing the plasmid TOXHH1

ATCC No.: n/a *E. coli* TG1 containing the plasmid TOXEE1

For the CAI protein:

ATCC No. 69158 *E. coli* TG1 containing the plasmid 57/D

ATCC No. 69159 *E. coli* TG1 containing the plasmid 64/4

ATCC No. 69160 *E. coli* TG1 containing the plasmid P1-24

ATCC No. 69161 *E. coli* TG1 containing the plasmid B/1

For the heat shock protein (hsp):

ATCC No. 69155 *E. coli* TG1 containing the plasmid pHp60G2

ATCC No. 69156 *E. coli* TG1 containing the plasmid pHp605.--

IN THE CLAIMS:

Please cancel claims 38, 39, 42, 44, 48, 50, 51, 53, 60, 61, 64-66, 71, 73, 74, 77, and 79 without disclaimer or prejudice to reintroduction at a later time.

Please amend claims 40, 45, 47, 54, 56, 57, 59, 62,63, 70, 75-76, 78, and 80 to read as follows:

40. (Twice amended) A purified polypeptide [of the *Helicobacter pylori* CAI antigen] comprising the amino acid sequence of SEQ ID NO:5.

45. (Three times amended) A purified polypeptide [of the *Helicobacter pylori* CAI antigen, which polypeptide: (i) comprises] comprising at least ten contiguous amino acids of SEQ ID NO:5, [(ii)] which polypeptide: (i) can be used to induce the production of antibodies to *Helicobacter pylori* CAI antigen, and [(iii)] (ii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity].

47. (Three times amended) The polypeptide of claim 45 which comprises at least fifteen contiguous amino acids of SEQ ID NO:5.

54. (Three times amended) A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a recombinant polypeptide [of the *Helicobacter pylori* CAI antigen], which recombinant polypeptide: (i) comprises at least ten contiguous amino acids of SEQ ID NO:5, (ii) can be used to induce the production of antibodies to *Helicobacter pylori* CAI antigen, and (iii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity].

56. (Three times amended) The vaccine of claim 54 wherein said polypeptide comprises at least fifteen contiguous amino acids of SEQ ID NO:5.

57. (Three times amended) The vaccine of claim 54 further comprising an immunologically effective amount of a second polypeptide [of the *Helicobacter pylori*

heat shock protein], which second polypeptide: (i) comprises at least ten contiguous amino acids of *Helicobacter pylori* heat shock protein, (ii) can be used to induce the production of antibodies to *Helicobacter pylori* heat shock protein, and (iii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity].

59. (Three times amended) The vaccine of claim 57 wherein said second polypeptide comprises at least fifteen contiguous amino acids of *Helicobacter pylori* heat shock protein.

62. (Three times amended) A method of preparing a prophylactic or therapeutic vaccine comprising bringing into association:

(1) an immunologically effective amount of a purified polypeptide [of the *Helicobacter pylori* CAI antigen amino acid], which polypeptide: (i) comprises at least ten contiguous amino acids of SEQ ID NO:5, (ii) can be used to induce the production of antibodies to *Helicobacter pylori* CAI antigen, and (iii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity], and

(2) a pharmaceutically acceptable carrier.

63. (Three times amended) The method of claim 62 or 78 further comprising adding an immunologically effective amount of a second polypeptide [of the *Helicobacter pylori* heat shock protein], which second polypeptide: (i) comprises at least ten contiguous amino acids of *Helicobacter pylori* heat shock protein, (ii) can be used to induce the production of antibodies to *Helicobacter pylori* heat shock protein, and (iii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity].

70. (Twice amended) The vaccine of claim 54 [48 or 79], further comprising an immunologically effective amount of a second polypeptide, wherein said second polypeptide [is of the *Helicobacter pylori* cytotoxin (CT) protein, and] (i) comprises at least ten contiguous amino acids of *Helicobacter pylori* cytotoxin (CT) protein, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) is

substantially noncytotoxic [exhibits substantially no toxicity, or substantially reduced toxicity].

75. (Amended) A recombinant polypeptide [of the *Helicobacter pylori* CAI antigen, which polypeptide: (i) comprises] comprising at least ten contiguous amino acids of SEQ ID NO:5, [(ii)] which recombinant polypeptide: (i) can be used to induce the production of antibodies to *Helicobacter pylori* CAI antigen, and [(iii)] (ii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity].

76. (Amended) The polypeptide of claim 75 which comprises at least fifteen contiguous amino acids of SEQ ID NO:5.

78. (Amended) A method of preparing a prophylactic or therapeutic vaccine comprising bringing into association:

(1) an immunologically effective amount of a recombinant polypeptide [of the *Helicobacter pylori* CAI antigen], which recombinant polypeptide: (i)comprises at least ten contiguous amino acids of SEQ ID NO:5, (ii) can be used to induce the production of antibodies to *Helicobacter pylori* CAI antigen, and (iii) is substantially noncytotoxic [exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity], and

(2) a pharmaceutically acceptable carrier.

80. (Amended) The vaccine of claim 70 wherein said second polypeptide comprises at least fifteen contiguous amino acids of *Helicobacter pylori* CT protein.

Please add the following new claims 81-139:

81. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids from SEQ ID NO:5.

82. (New) The polypeptide of claim 81, said polypeptide comprising at least ten contiguous amino acids from SEQ ID NO:5.

83. (New) The polypeptide of claim 81, said polypeptide comprising at least fifteen contiguous amino acids from SEQ ID NO:5.

84. (New) The polypeptide of claim 81, 82, or 83, said polypeptide further comprising *Helicobacter pylori* cytotoxin associated immunodominant (CAI) antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

85. (New) The polypeptide of claim 84, said polypeptide comprising an immunogenic fragment of *Helicobacter pylori* CAI antigen.

86. (New) The polypeptide of claim 84, said polypeptide comprising an immunogenic derivative of *Helicobacter pylori* CAI antigen.

87. (New) The polypeptide of claim 81, said polypeptide comprising amino acids 1-1147 of SEQ ID NO:5.

88. (New) The polypeptide of claim 84, wherein said polypeptide is a recombinant polypeptide.

89. (New) The polypeptide of claim 81, said polypeptide comprising *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen which is immunogenically identifiable with the protein encoded by SEQ ID NO:5.

90. (New) The polypeptide of claim 81, said polypeptide further comprising one or more amino acid substitutions or deletions, wherein said amino acid substitutions or deletions do not substantially affect the functional aspects of said antigen.

91. (New) The polypeptide of claim 90, wherein said amino acid substitution is a conservative amino acid replacement.

92. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids from SEQ ID NO:5 and further comprising SEQ ID NO:12.

93. (New) The polypeptide of claim 81, said polypeptide comprising at least five contiguous amino acids from amino acids 707-937 of SEQ ID NO:5.

94. (New) The polypeptide of claim 92, comprising at least ten contiguous amino acids of SEQ ID NO:5.

95. (New) The polypeptide of claim 92, comprising at least fifteen contiguous amino acids of SEQ ID NO:5.

96. (New) The polypeptide of claim 92, 94, or 95, further comprising *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

97. (New) The polypeptide of claim 96, comprising an immunogenic derivative of *Helicobacter pylori* CAI antigen.

98. (New) The polypeptide of claim 96, said polypeptide comprising an immunogenic fragment of *Helicobacter pylori* CAI antigen.

99. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids from SEQ ID NO:5 and further comprising one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:16, and SEQ ID NO:17.

100. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids from SEQ ID NO:5 and further comprising the amino acid sequence of SEQ ID NO:17.

101. (New) The polypeptide of claim 99 or 100, said polypeptide further comprising a *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

102. (New) The polypeptide of claim 101, said polypeptide comprising an immunogenic fragment of a *Helicobacter pylori* CAI antigen.

103. (New) The polypeptide of claim 101, said polypeptide comprising an immunogenic derivative of a *Helicobacter pylori* CAI antigen.

104. (New) The polypeptide of claim 99 or 100, wherein the polypeptide comprises at least ten contiguous amino acids from SEQ ID NO:5.

105. (New) The polypeptide of claim 99 or 100, wherein the polypeptide comprises at least fifteen contiguous amino acids from SEQ ID NO:5.

106. (New) The polypeptide of claim 99, said polypeptide comprising the amino acid sequence of SEQ ID NO:14.

107. (New) The polypeptide of claim 99, said polypeptide comprising the amino acid sequence of SEQ ID NO:16.

108. (New) The polypeptide of claim 99, said polypeptide comprising the amino acid sequence of SEQ ID NO:17.

109. (New) The polypeptide of claim 81, said polypeptide comprising at least amino acid positions 748 to 977 of SEQ ID NO:5.

110. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids from SEQ ID NO:5 and further wherein said polypeptide comprises one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:17, and SEQ ID NO:23.

111. (New) The polypeptide of claim 110, wherein said polypeptide comprises at least ten contiguous amino acids from SEQ ID NO:5.

112. (New) The polypeptide of claim 110, wherein said polypeptide comprises at least fifteen contiguous amino acids from SEQ ID NO:5.

113. (New) The polypeptide of claim 110, 111, or 112, said polypeptide further comprising a *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

114. (New) The polypeptide of claim 113, said polypeptide comprising an immunogenic derivative of a *Helicobacter pylori* CAI antigen.

115. (New) The polypeptide of claim 113, said polypeptide comprising an immunogenic fragment of a *Helicobacter pylori* CAI antigen.

116. (New) The polypeptide of claim 110, said polypeptide comprising the amino acid sequence of SEQ ID NO:9.

117. (New) The polypeptide of claim 110, said polypeptide comprising the amino acid sequence of SEQ ID NO:10.

118. (New) The polypeptide of claim 110, said polypeptide comprising the amino acid sequence of SEQ ID NO:17.

119. (New) The polypeptide of claim 110, said polypeptide comprising the amino acid sequence of SEQ ID NO:23.

120. (New) The polypeptide of claim 110, said polypeptide comprising at least five contiguous amino acids from amino acid position 600 to amino acid position 900 of SEQ ID NO:5.

121. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:12.

122. (New) An isolated immunogenic polypeptide comprising at least five contiguous amino acids of SEQ ID NO:17.

123. (New) An isolated immunogenic polypeptide encoded by at least fifteen contiguous nucleotides of SEQ ID NO:4.

124. (New) An isolated immunogenic polypeptide encoded by at least thirty contiguous nucleotides of SEQ ID NO:4.

125. (New) An isolated immunogenic polypeptide encoded by at least forty-five contiguous nucleotides of SEQ ID NO:4.

126. (New) The polypeptide of claim 123, 124, or 125, said polypeptide comprising *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

127. (New) The polypeptide of claim 123, said polypeptide encoded by the polynucleotide sequence of SEQ ID NO:4.

128. (New) The polypeptide of claim 126, wherein said polypeptide is a recombinant polypeptide.

129. (New) The polypeptide of claim 123, further encoded by the polynucleotide sequence of SEQ ID NO:11.

130. (New) The polypeptide of claim 123, said polypeptide encoded by at least fifteen contiguous nucleotides of nucleotide positions 2772-3466 of SEQ ID NO:4.

131. (New) The polypeptide of claim 124, further encoded by the polynucleotide sequence of SEQ ID NO:11.

132. (New) The polypeptide of claim 125, further encoded by the polynucleotide sequence of SEQ ID NO:11.

133. (New) The polypeptide of claim 129, 131, or 132, comprising *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

134. (New) The polypeptide of claim 123, further encoded by at least one or more of the polynucleotides sequences selected from the group consisting of SEQ ID NO:13, SEQ ID NO:15, and SEQ ID NO:18.

135. (New) The polypeptide of claim 134, comprising *Helicobacter pylori* CAI antigen, an immunogenic fragment of *Helicobacter pylori* CAI antigen, or an immunogenic derivative of *Helicobacter pylori* CAI antigen.

136. (New) The polypeptide of claim 124, further encoded by at least one or more of the polynucleotides sequences selected from the group consisting of SEQ ID NO:13, SEQ ID NO:15, and SEQ ID NO:18.

137. (New) The polypeptide of claim 125, further encoded by at least one or more of the polynucleotides sequences selected from the group consisting of SEQ ID NO:13, SEQ ID NO:15, and SEQ ID NO:18.

138. (New) The polypeptide of claim 99, said polypeptide comprising the amino acid sequence of SEQ ID NO:10.

139. (New) An isolated immunogenic polypeptide comprising the amino acid sequence of SEQ ID NO:10.